expressed therein and add new claims 15-35 as indicated in Appendix A submitted herewith. Appendix A is a clean copy of the new claims.

REMARKS

Claims 15-35 are currently pending in the present application. The claims have been amended in the expectation that the amendments will place this application in condition for allowance. Additionally, applicants present herein a check for $18.00 for the addition of one additional claim over twenty total claims. The amendments do not introduce new matter within the meaning of 35 U.S.C. §132. Accordingly, entry of the amendments is respectfully requested.

1. Rejection of Claims 1, 3, 5-8, and 13-14 for Obviousness-Type Double Patenting

The Official Action states that claims 1, 3, 5-8, and 13-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,087,489.

It should be noted that as the prosecution of this application is not closed, any arguments and comments made herein are made without prejudice to, or disclaimer of, any additional or different amendments, arguments, or comments as may be offered during the continuing prosecution of this

application, as well as any divisional filing(s) or continuation(s) of this application.

Applicants respectfully traverse the obviousness-type double patenting rejection over U.S. Patent No. 6,087,489, on the ground that the instant claims are patentable under the proper one-way obviousness determination. The one-way test is proper since the present application has the later effective U.S. filing date (See MPEP § 804).

Traversal: One-Way Obviousness Determination

Under a one-way obviousness determination, an obviousness-type double patenting rejection is improper where the application claims are patentably distinct from the prior patent claims.

A. The claimed subject matter

The present invention relates to antisense deoxyoligonucleotides that hybridize to a target 3′ region of a mammalian thymidylate synthase nucleic acid, as well as compositions and methods of using these antisense deoxyoligonucleotides. In particular, the application claims relate to compositions containing an antisense deoxyolignucleotide having a sequence according to SEQ ID No. 1 or SEQ ID No. 2, methods of using these compositions to treat

cancer, methods of using the antisense deoxyoligonucleotides having a sequence according to SEQ ID No. 1 or SEQ ID No. 2 to inhibit thymidylate synthase expression in mammalian tumor cells, combination products of the antisense deoxyoligonucleotides having a sequence according to SEQ ID No. 1 or SEQ ID No. 2 in combination with an anticancer agent, and methods of using these combination products to treat cancer.

B. The claims of the '489 patent

In contrast, the '489 patent claims an antisense oligonucleotide 8 to 30 nucleotides in length comprising a nucleotide sequence complementary to a nucleic acid molecule encoding human thymidylate synthase, wherein said oligonucleotide is complementary to the 3' untranslated region of said nucleic acid molecule and inhibits the expression of said human thymidylate synthase. The oligonucleotide can have SEQ ID Nos. 2, 3, 4, 5, or 6 according to claims 2 and 9. SEQ ID Nos. 1 and 2 of the present application are not specifically recited in the '489 patent claims.

C. The differences between the claimed subject matter and the claims of the '489 patent

Contrary to the Office Action, the '489 patent does not contain claims having the present inventive subject matter. In this regard, applicants note that obviousness-type double

patenting only occurs where the subject matter claimed in a later application is not patentably distinct from the subject matter claimed in a commonly owned earlier patent. See Ex parte Davis, 56 U.S.P.Q.2d 1434, 1435-36 (Bd. Pat. Int. 2000). "A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim." Eli Lilly & Co. v. Barr Labs, Inc., 58 U.S.P.Q.2d 1869, 1878 (Fed. Cir. 2001).

The present invention is patentably distinct from the claims of the '489 patent. In particular, the application claims relate in a preferred embodiment to compositions containing and methods of using two specific antisense deoxyoligonucleotides, i.e. those having SEQ ID No. 1 or SEQ ID No. 2. None of the claims of the '489 patent recite these two specific sequences. Accordingly, the application claims are not anticipated by the claims of the '489 patent.

Further, the claims of the '489 patent do not render obvious the application claims. In particular, the application claims relate in a preferred embodiment to two specific antisense deoxyoligonucleotides, i.e. those having SEQ ID No. 1 or SEQ ID No. 2. In contrast, the claims of the '489 patent relate to "An antisense oligonucleotide 8 to 30 nucleotides in

length…, wherein said oligonucleotide is complementary to the 3′ untranslated region of said nucleic acid molecule and inhibits the expression of said human thymidylate synthase." At best, the two specific sequences required by the application claims are species falling within the genus claimed by the '489 patent. It is a well-settled part of U.S. law that a later species is patentably distinct from, and non-obvious over, an earlier genus.

In this regard, applicants note that where an earlier genus has a relatively large number of substituents that can be made, a showing of obviousness is not so readily accomplished. The fact that a claimed compound may be encompassed by an earlier generic structure does not by itself render that compound obvious. *In re Jones*, 21 U.S.P.Q.2d 1941, 1943 (Fed. Cir. 1992). Where there is a selection to be made among the genus taught by the prior art, the prior art reference must provide a motivation to make the proper selection to arrive at the target compound. *In re Baird*, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994). Accordingly, since the '489 patent claims provide no motivation to select the two specific sequences required by the application claims from the disclosed genus of antisense oligonucleotides 8 to 30 nucleotides in length, the application claims are not

obvious over the '489 patent claims as alleged by the Examiner.

Regarding the Examiner's statement that "the antisense compound according to SEQ ID NO: 1 and 2 recited in claim 3 of the instant application are species of the broad genus of antisense compounds recited in claim 1 of the referenced US Patent, such that the antisense compounds recited in claim 3 of the instant application anticipates the genus of issued claim 1", applicants respectfully assert the Examiner is incorrectly applying a two-way test for obviousness in reaching this conclusion.

As noted above, a one-way test, rather than a two-way test, is presently proper since the present application is the later filed application as compared to the '489 patent (See MPEP § 804). Under the one-way test, the only relevant inquiry is whether the application claims are patentably distinct from the prior patent claims. It is irrelevant whether the application claims anticipate the earlier patent claims, as asserted by the Examiner.

Regarding the Examiner's assertion that the application claims "can not be considered patentably distinct over claims 1-10 of the issued US Patent when there are specifically disclosed embodiments in US Patent 6,087,489 which clearly indicate that

claims...of the instant application are merely obvious variations of the invention of claims 1-10 of the referenced patent", the Examiner is reminded that only the claims of the respective patent and application are relevant to an obviousness-type double patenting inquiry. The disclosed embodiments of the '489 patent noted by the Examiner are irrelevant in determining whether there is obviousness-type double patenting; rather, the focus is on the claims of the '489 patent.

Since the application claims are not anticipated by, or obvious over, the claims of the '489 patent as shown above, the application claims are patentably distinct from the claims of the '489 patent. There is no obviousness-type double patenting over the claims of the '489 patent.

Additionally, applicants note that several claims have been cancelled from the present application merely to speed prosecution of this application. In so doing, applicants make no admission that the subject matter of the cancelled claims is unpatentable in view of the outstanding present rejection and do not prejudice any attempts to further prosecute the cancelled subject matter or any other alternative or broader claims in a later continuing application.

Accordingly, applicants respectfully request the Examiner

to reconsider and withdraw the rejection of pending claims 15-35.

2. Rejection of claims 9 and 11 under 35 USC 112, first paragraph

Claims 9 and 11 stand rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record set forth in the Official Action mailed January 31, 2001.

Applicants point out to the Examiner that claims 9 and 11 have been cancelled, rendering the present rejection moot.

CONCLUSION

Based upon the foregoing amendments and remarks, the presently claimed subject matter is believed to be enabled, novel, and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the outstanding rejections and allow all pending claims 15-35 presented herein for reconsideration. Favorable action with an early allowance of the pending claims is earnestly solicited.

The Examiner is invited to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,

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BOX PATENT
Attorney Docket No. 24911

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

KOROPATNICK et al.

Examiner: J. Epps

Serial No.: 09/509,418

Art Unit: 1635

Filing Date: July 11, 2000

For: **ANTISENSE OLIGONUCLEOTIDES AGAINST THYMIDYLATE SYNTHASE**

Appendix A

Please cancel all pending claims 1, 3, 5-9, 11, 13, and 14 and add new claims 15-35 as indicated in the following clean copy of the new claims.

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15. (New) A composition comprising an antisense deoxyoligonucleotide having a sequence according to SEQ ID No. 1 or SEQ ID No. 2 and a pharmaceutically acceptable carrier or diluent.

16. (New) The composition according to claim 15 for use in combination with a thymidylate synthase inhibitor.

17. (New) The composition according to claim 16, wherein the thymidylate synthase inhibitor is Tomudex.

18. (New) The composition according to claim 15 for use in combination with an antiproliferative drug.

19. (New) The composition according to claim 18, wherein the anti-proliferative drug is selected from the group consisting of: methotrexate, 5-fluorouracil, FUdR, ftorafur, and FdUR.

20. (New) The composition according to claim 15, wherein the composition is in a conventional dosage form selected from the group consisting of: oral, topical, nasal, vaginal, rectal, inhalation, sub-lingual, buccal, and parenteral dosage forms.

21. (New) A method for inhibiting thymidylate synthase expression in mammalian tumor cells, comprising: administering to the mammalian tumor cells an antisense deoxyoligonucleotide having a sequence according to SEQ ID No. 1 or SEQ ID No. 2, wherein the antisense deoxyoligonucleotide hybridizes to a target 3′ untranslated region of a mammalian thymidylate synthase nucleic acid and inhibits thymidylate synthase expression in said mammalian tumor cells.

22. (New) The method according to claim 21, wherein said antisense deoxyoligonucleotide is administered in an amount sufficient to inhibit tumor cell growth.

23. (New) The method according to claim 21, wherein said antisense deoxyoligonucleotide is administered in an amount sufficient to inhibit tumor cell proliferation.

24. (New) The method according to claim 21, wherein said antisense deoxyoligonucleotide is administered in an amount sufficient to sensitize mammalian tumor cells to an anticancer agent.

25. (New) The method according to claim 24, wherein the anticancer agent is selected from the group consisting of: a thymidylate synthase inhibitor, a cytostatic agent and an antiproliferative drug.

26. (New) The method of according to claim 24, wherein the anticancer agent is selected from the group consisting of Tomudex, methotrexate, 5-fluorouracil, FUdR, ftorafur, and FdUR.

27. (New) The method according to claim 21, wherein the mammalian tumor cells are human tumor cells.

28. (New) The method according to claim 27, wherein the human tumor cells are selected from the group consisting of human breast cancer cells and human cervical cancer cells.

29. (New) A combination product comprising an antisense deoxyoligonucleotide having a sequence according to SEQ ID No. 1 or SEQ ID NO. 2 in combination with an anticancer agent, wherein the antisense deoxyoligonucleotide hybridizes to a 3' untranslated region of a mammalian thymidylate synthase nucleic acid and inhibits thymidylate synthase expression in mammalian cells.

30. (New) The combination product according to claim 29, wherein the anticancer agent is selected from the group consisting of: a thymidylate synthase inhibitor, a cytostatic agent, and an antiproliferative drug.

31. (New) The combination product according to claim 29, wherein the anticancer agent is selected from the group consisting of Tomudex, methotrexate, 5-fluorouracil, FUdR, ftorafur, and FdUR.

32. (New) The composition according to claim 15, wherein the deoxyoligonucleotide is phosphorothioated, methoxy-ethoxy winged or contains a peptide nucleic acid backbone.

33. (New) The combination product according to claim 29, wherein the deoxyoligonucleotide is phosphorothioated, methoxy-ethoxy winged or contains a peptide nucleic acid backbone.

34. (New) A method for the treatment of cancer or for providing an anti-proliferative effect comprising administering to a human an effective amount of the composition of claim 15.

35. (New) A method for the treatment of cancer or for providing an anti-proliferative effect comprising administering to a human an effective amount of the combination product of claim 29.